EXHIBIT B

Expert report
Sheila Weiss Smith, Ph.D., FISPE

My Background and qualifications:

I am currently an Associate Professor in the Department of Pharmaceutical Health Services Research, School of Pharmacy, with a secondary appointment in the Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland, Baltimore, MD, and an affiliate appointment in the Gerontology doctoral program (University of Maryland Baltimore and University of Maryland Baltimore County). I am also a Visiting Associate Professor (each summer since 2005) at the Bloomberg School of Public Health, Johns Hopkins University, where I teach a course in Pharmacoepidemiology. I hold appointments at the U.S. Food and Drug Association (special government employee) and the U.S. Veterans Administration (research associate).

I earned a B.S. in Biology from the University of Maine in 1981, a M.S. in Exercise Sciences from Northeastern University (Boston, MA) in 1986 and a Ph.D. in Epidemiology from Johns Hopkins University in 1996. I completed a two-year postdoctoral fellowship in Pharmacoepidemiology & Regulatory Sciences at the U.S. Food and Drug Association and University of Maryland. I was inducted in the honor societies for both Education (Kappa Delta Pi) and Pharmacy (Rho Chi) and am a fellow of the International Society of Pharmacoepidemiology.

My research efforts and writings have focused on the area of pharmacoepidemiology, and I have written on the epidemiology of the risks associated with prescription medications with a special emphasis on methodology. I am currently principle investigator of a one-half million dollar grant "the value of data mining", which is an extensive look at the comparative validity of data mining algorithms in the FDA's adverse reporting database, industry practices in data mining, and factors which influence the results of data mining. Additionally, I have been Principal Investigator of two sequential NCI contracts to look at the strength of the scientific evidence for cancer prevention and cancer promotion among commonly used medicines and nutraceuticals, and to estimate the potential public health impact. I am on the executive committee of the University of Maryland's DeCIDE center, which is an AHRQ project (Bruce Staurt, PI), and an investigator on grants from NIDDK (Jeff Fink, PI) and Sanofi-Adventis (Daniel Mullins, PI). Past funding including grants and contracts from the FDA, NASA, the Pfieffer Foundation, Drug Information Association, Glaxo-Smith Klein, etc. are listed in my C.V. I have published more than 30 peer-reviewed papers (with in excess of 570 citations), a number of which in high impact journals including New England Journal of Medicine, British Medical Journal, and Pharmacoepidemiology and Drug Safety (PDS). One paper (Cluxton et al, 2005) was awarded the annual prize for best paper in PDS, for the year 2005. I am author or coauthor of more than 50 scientific presentations/posters and have given approximately 30 invited talks. I am an active member of the International Society of Pharmacoepidemiology; participating in annual meetings, chairing sessions, reviewing abstracts, and serving on a number of

committees. I have also held elected positions including membership on the board of directors. Currently, I teach a course "advanced topics in pharmacoepidemiology", an advanced level doctoral course which is offered biannually. This year it is being taught simultaneously at the University of Maryland and at the FDA. I also teach a course in epidemiology to the pharmacy students and a course in Pharmacoepidemiology at Johns Hopkins University annually. I regularly lecture in pharmacoepidemiology and epidemiology courses run by other faculty at the University of Maryland and at Yale University. I have served as a special government employee for the FDA, over a span of more than a dozen years, and participated on a number of advisory committees as a voting member. Most recently, in 2007 I served on the FDA's antiretroviral advisory committee where we reviewed Pfizer's application for approval of maraviroc. I have reviewed grant proposals for the FDA, AHRQ, and EMEA and serve as a peer-reviewer for a large number of journals including Lancet, British Medical Journal, and PDS. I am on the editorial board of the Journal of Research in Social and Administrative Pharmacy and Isotretoin Scientific Advisory Board.

My experience and training are summarized in my CV, a copy of which is incorporated by reference and attached as Exhibit A.

I hold the opinions expressed below are held to a reasonable degree of scientific certainty.

My prior testimony as an expert within the past 4 years:

- Fisk v. Novartis, Dist. of Utah, Central, 2005

My fee schedule is $400 per hour.

My opinions in this matter are derived from a review of the materials described in the appendix, as well as my education, training, experience, and materials and information seen or considered in the course of my professional activities. I have been asked to evaluate the available epidemiologic evidence concerning whether Neurontin is associated with suicidal behavior, including suicide and suicide attempt. To answer this question I have considered the randomized controlled clinical trial data, the uncontrolled clinical trial data, epidemiology studies, peer-reviewed literature, and information from FDA's AERS database. I have also been asked to consider aspects of plaintiffs' expert reports and depositions asserting that Neurontin is a cause of suicide and suicide attempt. In answering these questions I have applied generally accepted pharmacoepidemiologic principles. These are the same principles that I apply in the course of professional activities, including teaching pharmacoepidemiology, publishing peer-reviewed papers and advising public health agencies such as FDA as to the risks associated with various medicines.

I reserve the right to review, consider and rely upon reports and materials considered by other designated experts in this litigation.

In summary, it is my opinion to a reasonable degree of scientific certainty that there is no reliable evidence that Neurontin is a cause of suicide or suicide attempt. In considering the totality of the pharmacoepidemiologic evidence it is my opinion that Neurontin is not a cause of suicide or suicide attempt. The opinions of Plaintiffs' experts, Dr. Cheryl Blume and Dr. Sander Greenland, do not establish through any recognized methodology that Neurontin causes, or even increases the risk for, suicide or suicidal behavior. One expert (Dr. Blume) purports to use epidemiologic evidence in support of a causation opinion, the other (Dr. Greenland) essentially finds there is no epidemiologic evidence to permit any valid conclusions concerning these questions. As set forth below, multiple lines of epidemiologic evidence, when examined according to appropriate epidemiologic methods and pursuant to public health protocols, consistently demonstrates that Neurontin neither causes nor is associated with an increased risk of suicide or suicide attempt.

Pharmacoepidemiology

Pharmacoepidemiology is the study of the use and effects of medical products (drugs, biologicals, and medical devices) in human populations. It has emerged as a unique branch of epidemiology over the past several decades, distinguished from other field by the focus on medical product as the risk factors or exposures. Pharmacoepidemiology studies the adverse drug effects and adverse drug events, and assists in making important regulatory and public health judgments concerning the risks and benefits of medicines. Weiss Smith S. Chapter Title: Pharmacoepidemiology. In: *Encyclopedia of Epidemiology.* Editor: Boslaugh S. Publisher: Sage Publications Inc. 2007.

Pharmacoepidemiological investigations utilize the methods and study designs of epidemiology. The field relies heavily on the use of existing databases; health care service utilization data, automated medical records, and health care and pharmaceutical claims. Databases have a distinct advantage over original data collection in the speed it takes to complete a study as well as the size of the underlying population. However, each database has distinct characteristics that can impact internal and external validity of a study. Knowledge of database characteristics, local medical practice, and the covered population, and how these unique database characteristics influence the potential of being prescribed a particular drug and the likelihood of diagnosing the study outcome, are critical to designing a valid epidemiological study. Weiss Smith S. Chapter Title: Pharmacoepidemiology. In: *Encyclopedia of Epidemiology.* Editor: Boslaugh S. Publisher: Sage Publications Inc. 2007.

Medical products are regulated by government entities; they are approved for a specific use or indication with specific dosing and instructions for use. Exposures to medical products are made consciously, for the treatment of a known medical condition or to prevent or delay the occurrence of a disease. The deliberate nature of medication choice, often introduces biases into observational studies, which can make comparisons of exposed with a comparison drug or no drug (unexposed) inappropriate. Weiss Smith S.

Chapter Title: Pharmacoepidemiology. In: *Encyclopedia of Epidemiology.* Editor: Boslaugh S. Publisher: Sage Publications Inc. 2007. The most common of these biases, called "confounding by indication" drives many research design decisions and ultimately impacts interpretation of study results. Salas, *et al.* Confounding by Indication: An Example of Variation in the Use of Epidemiologic Terminology. *American Journal of Epidemiology.* 1999;149(11):981-983., Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm. Because of the potential for spurious results, the FDA guidance document states: "Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different design. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm -p.13

The scientific method for causal assessment

We would like to know the absolute truth about the causal relationship between an exposure and an adverse event, or for that matter between a medicine and its positive effects. However, research studies never "prove" causality, no matter how good the study. Pharmacoepidemiologic research provides scientific support to make reliable inferences/judgments based on statistical associations. The analysis of a scientific study provides statistics that tell us about the existence of an association, the strength or magnitude of the association, and the probability of whether it is due to chance (random error). By virtue of the inherent variability of human experimentation, it is necessary for scientists and regulatory agencies to make medical and regulatory decisions about drugs in the absence of perfect information. Once an association is established, the totality of the evidence is weighed in a process called causal assessment. The process of causal assessment is well established in the medical field and causal criteria are included in textbooks of epidemiology. Ann Aschengrau, George R. Seage, ScD, *Essentials of Epidemiology in Public Health,* Jones & Bartlett 2nd ed. 2007.

The Reference Manual on Scientific Evidence sets forth the generally accepted methodology for proving general causation. Federal Judicial Center, Reference Manual on Scientific Evidence, 2 ed. (2000). The first and most critical step in this process is demonstrating that there is an association between the exposure and the outcome. Michael D. Green et al, *Reference Guide on Epidemiology, in* Reference Manual on Scientific Evidence, 333, 337, 348 (2d ed. 2000). An experimental study is considered the best scientific evidence because all factors except for the experimental agent are controlled. In human studies, the randomized clinical trial ("RCT") is the gold standard

for determining an association between an exposure and an outcome. A hallmark of clinical trials is that the patients are randomized to receive the drug or a placebo (or in some cases another agent). This ensures that there is no bias in determining who gets the treatment under study. Also, in RCTs substantial efforts are made to ensure that the protocol is followed closely and participants are treated and monitored similarly in all respects expect for the exposure to the study drug. RCTs are required as evidence that the drug has the intended effect and are heavily relied upon by the FDA to make the risk-benefit assessment, which forms the basis for drug approval.

Other types of epidemiological studies are observational in nature. Observational study designs include cohort studies, cross-sectional studies, case-control studies, and ecological studies. Observational studies can be used to determine if there is a statistical association between and agent and an outcome. However, because patients are not randomized to treatment as well as other factors in their design and execution, they are more subject to biases and confounding factors which may obscure a true effect or create a false association, when there is no effect. Therefore, they are considered as lesser evidence of a causal association than a RCT. Case reports cannot be used to establish an association, because they lack a control or comparison group; they are merely reports of occurrences of an outcome. David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, *in* Reference Manual on Scientific Evidence 83, 90-91 (2d ed. 2000).

The presence of a statistical association does not mean that an agent causes the disease or outcome of interest. U.S. Dep't of Health & Human Servs., *Mental Health: A Report of the Surgeon General* 51 (1999). Instead, if a statistical association is established, determining the likelihood of a true casual relationship is a process of inference. As stated by the U.S. Surgeon General in 1964, "if it be shown that an association exists, then the question is asked: 'Does the association have a causal significance?" U.S. Dep't of Health, Educ. & Welfare, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* 20 (1964). This concurs with the Reference Manual on Scientific Evidence, "Once an association has been found between an exposure to an agent and the development of a disease, researchers consider whether the association reflects a true case-effect relationship." Reference Manual on Scientific Evidence at 526. If an association is not found, the process of causal assessment ends there.

The process of attributing causation of an adverse drug effect to a specific agent is a judgment call. Once a statistical association has been detected and confirmed using appropriate methodology, the next step in the process is to consider the validity of the study and the potential for bias and/or confounding to have caused a spurious association. Studies can have flaws in design, conduct, and/or analysis that invalidate the results. Once an association has been established and the underlying studies are determined to be scientifically valid, the next step is to conduct a causal assessment. A generally accepted methodology for determining whether an association is potentially causal is the application of the "Bradford-Hill Criteria." These criteria include (1) temporal relationship; (2) strength of association; (3) dose-response; (4) replication of the results; (5) biological plausibility; (6) consideration of alternative explanations; (7) cessation of exposure; (8) specificity of exposure; and (9) consistency with other knowledge.

Bradford-Hill, The environment and disease: Association or causation Royal Soc'y Med 295,295-96(1965).

Not all of these criteria must be met for there to be a true causal effect, however, the criteria of temporality is absolutely required. **Temporality** in this context means that the exposure must come before the outcome. Epidemiological study results are often presented as a relative comparison of outcomes rates or risks among those with exposure to those without exposure; which include relative risks, odds ratios, and proportional (relative) hazards. **The strength of the association** refers to the magnitude of this measure; the more extreme the value (from a ratio of 1.0) the greater the likelihood that it could be a causal relationship. (Reference Manual on Scientific Evidence at 528-29 Brad ford hill – the environment and disease: Association or causation Royal Soc'y Med 295,295-96(1965). A dose-response relationship means that the greater the exposure, the higher the relative risk. **A dose-response relationship** means that the greater the dosage (or intensity) of exposure, the higher the risk, or possibly the severity, of the outcome. A dose-response relationship can add strength to the argument for causality. **Replication of results** across studies, particularly in different populations by different investigators is also important, as any one study find an association just by random chance or because of a unique study population. **Biological plausibility**, in that the association makes sense, in light of other types of information available in the literature. However, "as important as we consider biological plausibility to be, it is equally important to realize that it can mislead in either direction." (Strom, 4th Ed., Chapt. 26, p. 395). **Consideration of alternative hypotheses** should be conducted early in the process of causal assessment. It is critical to consider the statistical association and if there are factors in the design or execution of the study that may have caused a spurious association. **Cessation of exposure** is based on the expectation that if an agent is the cause of a disease, its elimination from the population reduces the incidence of disease (e.g., incidence of lung cancer reduced when cigarette smoking reduced) (Reference Manual on Scientific Evidence at p. 378). **Specificity of exposure** is seen when the outcome is extremely rare (or non-existent) without the exposure, and is powerful evidence for causality. Associations that are **consistent with other knowledge** – such that they do not seriously conflict with generally known facts of the natural history and underlying biology of the disease – are also evidence for causality.

Pharmacoepidemiology of neurontin and suicide

A. Risk of suicide

Unfortunately, suicide and suicide attempt are not uncommon in this country. Intentional self-harm or suicide is ranked as the 11th most common cause of death in the United States
http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimdeaths05/prelimdeaths05.htm
The Centers for Disease Control and Prevention received 31,769 reports of suicide deaths in 2005. The death rate was 10.7 per 100,000 population. The rate of suicide

deaths increases with age. (Table 1) Suicide ranked among the top 5 most common causes of death for all age groups between four and 64 years old.

Table 1. Ranking of suicide as a cause of death by age groups, 2005 preliminary vital statistics data, United States.

Characteristic	Ranking as cause of death	Rate per 100,000 population
Age group		
4-15 years	5	0.7
15-24 years	3	9.8
25-44 years	4	13.4
45-64 years	8	14.9

Source Centers for Diease Control. Hsiang-Ching Kung, Ph.D.; Donna L. Hoyert, Ph.D.; Jiaquan Xu, M.D.; Sherry L. Murphy, **Deaths: Preliminary Data for 2005**. B.S. Division of Vital Statistics This report from the Centers for Disease Control and Prevention's. September 2007. available at:
http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimdeaths05/prelimdeaths05.htm

B. Neurontin

Neurontin was first approved for marketing in the United States in December 1993 as adjuvant (add-on) therapy for partial seizures in adults. Drugs@FDA Accessed: December 17, 2007. In October 2000, the FDA approved the drug for adjuvant therapy for the treatment of partial seizures in pediatrics, aged 3 years and older. Katz letter to Ms. Turner at Pfizer. October 12, 2000. http://www.fda.gov/cder/foi/appletter/2000/21216ltr.pdf. In 2002, the FDA approved an additional indication, postherpetic neuralgia in adults. Katz letter to Dr. Scott at Parke-Davis. http://www.fda.gov/cder/foi/nda/2002/21-397.pdf_Neurontin_Approv.pdf. Suicides and suicide attempts are elevated among persons with epilepsy and chronic pain. Neurontin is prescribed for the treatment of epilepsy, post-herpetic neuralgia as well as other conditions including chronic pain, anxiety disorder, and bipolar disorder.

It is generally understood that the patients for whom Neurontin is prescribed are at greater risk for suicidal behavior than the general population. Among patients with epilepsy the annual incidence of suicide is estimated at 0.035 to 0.075%, compared to 0.01% in the general population. Pfizer_MPatel_0039743. Thus patients with epilepsy are at a risk of suicide that is 3.2 times higher than the general population. In patients with epilepsy with comorbid psychiatric disease, the incidence of suicide increases further to 13.7 times higher than the general populations. Christensen, *et al.*, Epilepsy and risk of suicide: population-based case-control study. *Lancet* 6:693 – 698 (2007). Patients with bipolar disorder have a particularly high rate of suicide; 395 suicides per 100,000 patients each year. This rate is 36.4 times higher than the general population. Tondo L. *et al.* Suicidal Behaviour in Bipolar Disorder: Risk and Prevention. *CNS Drugs* 17:491-511 (2003).

The rates of suicide attempts are also elevated among patients with conditions that are commonly treated with gabapentin. For example, the annual rate of suicide attempts in the general US populations is 0.4%. Kessler, et al., Trends in Suicide Ideation, Plans, Gesturem and Attempts in the U.S. 1990 - 1992, to 2001 – 2003. *JAMA* 293:2487 – 2495 (2005) and the lifetime prevalence of suicide attempts is 4.6%. Kessler, et al, Prevalence of and risk factors for lifetime suicide attempts in the national comorbidity survey. *Arch. Gen. Psych.* 56:617 – 626 (1999). It has been established that there are 10 -25 suicide attempts for every suicide completion. Maris, Suicide. *Lancet* 360:319-26 (2002). Patients with epilepsy are at five times the risk of a suicide attempt. Hawton, et al., Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J. Clin. Psychiatry* 66:693 – 704 (2005), which is consistent with an estimated rate of suicide attempts of 2% per year. There have been a number of studies comparing suicide attempt rates among patients with chronic pain to controls without pain. While the lifetime prevalence of suicide attempts varied among across studies (range 5-13.7%), patients with pain were consistently were 2-3 times more likely have attempted suicide than those without pain. Tang and Crane, Suicidality in chronic pain: a review of the prevelance, risk factors and psychological links. *Psychol. Med.* 36:575 - 586 (2006).

A. Clinical Trial Analysis Pertaining to Suicide

i. Evertsz letter – June 2006

In March 2005, the FDA asked all AED manufacturers, including Pfizer to analyze its randomized controlled clinical trials to identify any possibly suicide-related events. The protocol for this analysis was determined by the FDA and modeled after the agency's analysis of SSRI medications. Correspondence from Russell G. Katz, M.D., Division Director, Division of Neurology Products, Center for Drug Evaluation and Research, FDA to Pfizer (March 16, 2005). Case identification included, among other things, an evaluation of all death reports to determine if the death could be attributed to suicide. To avoid bias, the medical reviewers were blinded to whether the person had received Neurontin or placebo. Using search strategies stipulated by FDA for "possibly suicide-related" adverse events that occurred in the double-blind phase of treatment or within one day of being taper, switching or stopping treatment. Response to FDA Suicidality Request (June 22, 2006), Pfizer_MEvertsz_0079431. Trained and qualified Pfizer psychiatrists reviewed and classified narratives, in a blinded fashion, using the approach from the Columbia University group (a well-accepted classification system for suicide analysis). *Id.;* Columbia Classification Algorithm of Suicide Assessment (C-CASA): Posner et al. *Am J Psychiatry.*2007; 164: 1035-1043. Fifty-two randomized clinical studies were identified for inclusion in the analysis of suicide and suicide attempt with Neurontin. Of these, two were excluded because all of the patients were three years old or younger and one because it was not a placebo-controlled (or low dose comparator). Among the studies that met FDA inclusion criteria there were 8829 subjects (including patients and volunteers); 5194 treated with Neurontin, 2682 treated with placebo, 661 treated with an active control and 292 treated with "low-dose" placebo. *Id.* The results of the blinded reviews and classifications revealed that there were no cases of suicide or suicide attempts among the study participants. With respect to suicidal ideation, 0.039

percent of patients treated with Neurontin reported suicidal ideation compared to 0.037 of patients on placebo. *Id.*

Pfizer concluded that "the currently submitted data provides further support for the conclusion that Neurontin neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture, and suicide ideation. While the population of patients who use gabapentin is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of gabapentin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with gabapentin." *Id.*

This reevaluation of the randomized clinical trial data is important in that there were no reports of suicides or suicide attempts despite more than 5000 Neurontin exposed patients, who are at elevated risk of suicide compared to the general population. I concur with Pfizer's conclusions, as set forth above, that these data provide no indication of an elevated risk of suicide or suicide attempt and, rather, demonstrates an absence of increased risk.

ii. Parson's Report – September 9, 2004 Response to FDA Regarding Suicide and Suicide Attempt in Neurontin (gabapentin) Clinical Trials and Postmarketing Surveillance

In 2004, FDA requested Pfizer to conduct a comprehensive search of gabapentin clinical trials and postmarketing databases across all patient populations for cases of suicide and suicide attempt. Response to FDA: Neurontin (September 9, 2004) Pfizer_MPatel_0039110. This analysis was completed and provided to FDA in September, 2004, ("Parson's Report"). FDA and Pfizer established a protocol to identify and analyze all reports of suicide or suicide attempt accumulated in the clinical trial databases for Neurontin. The methods are similar to the methods described above under the Evertsz June 2006 correspondence. *Id.* Among the differences with the June 2006 submission is that the protocols for the 2004 analysis did not employ the Columbia Suicidality Classification Project protocols. *Id.* Accordingly, the FDA in 2004 only requested data on suicides and suicide attempts, as opposed to data on intentional self-injury and suicidal ideation. A second difference regarding the protocols was that in the 2004 analysis all intentional overdoses were automatically categorized as a suicide or suicide attempt, whichever event applied, without any additional analyses. *Id.* A third difference is that the 2004 analysis was not limited to placebo-controlled clinical trials. *Id.* The Parson's Report summarizes the number and rates of suicide and suicide attempt across 92 clinical trials, phases 2-4. In this report the clinical trials are separated into those in which Neurotontin was compared to placebo and those in which there is no comparison group (open label). *Id.*

The placebo-controlled clinical trials were conducted for a variety of clinical indications including psychiatric conditions, neurological conditions, epilepsy, pain, and neuropathic pain. There were 2 cases of completed suicide in gabapentin-treated subjects (none in

placebo-controlled studies, one in non-placebo-controlled studies, and one that occurred 6 months post-treatment) and none in the placebo-treated subjects. *Id.* There were 12 cases of suicide attempt in gabapentin-treated subjects (one in placebo-controlled and 11 in non-placebo-controlled studies), of which 11 subjects were participating in epilepsy studies and 1 case involved a subject in a neuropathic pain study. *Id.*

Pfizer concluded, "In summary, the combined results of a comprehensive search for cases of suicide and suicide attempt among gabapentin clinical trials and postmarketing data across all patient populations did not indicate an increased risk of suicide with gabapentin treatment. The results of this review are consistent with the published literature for suicide in comparable patient populations in which gabapentin has been studied or used. No changes in the current product labeling, which currently includes suicidal and suicidal gesture in the clinical trial adverse event section, are necessitated by these findings." *Id.* at p. 2).

I concur with the Pfizer conclusion that the data from the clinical trials show that, regardless of indication, that there was no association between Neurontin and suicide or suicide attempt. There were no suicides or suicide attempts in the placebo-controlled clinical trials. In the context of uncontrolled trial data, it is appropriate methodology to consider and contrast these results against background rates of suicidal behavior in similar populations that are obtained from the peer-reviewed published literature. I disagree with Plaintiffs' expert, Cheryl Blume, that FDA "prohibits" such comparisons. In fact, in assessing risk, such comparisons are commonly used and recommended by FDA . Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm -p.11).

iii. Patel Letter, November 19, 2004 Re: "Generalized information – Reponse to the FDA regarding Suicide and Suicide Attempt in Neurontin (gabapentin) Phase I studies in electronic format.

This report was the second part of the analysis of all clinical studies and postmarketing data on Neurontin and suicide/suicide attempt. The Patel letter contained the analysis of the 55 Phase I studies that had been previously submitted or would be submitted for regulatory review (IND, NDA, sNDA). . Response to FDA Regarding Suicide and Suicide Attempt in Neurontin Clinical Trials – Phase 1 Studies (November 19, 2004) Pfizer_MPatel_0045143. The methods were the same as those described in the Parson's Report. The study subjects were predominantly health volunteers, though 10 studies were conduct in patients, including one long-term (>1 year) efficacy study of patients with epilepsy. There were no cases of suicide or suicide attempts in any of the placebo-controlled and non-placebo-controlled Phase I studies in healthy volunteers. Pfizer concluded that these data did not change the conclusions from the September 2004 Parson's Report.

B. Published literature

i. Collins and McFarland Article

"Divalproex, lithium and suicide among Medicaid patients with bipolar disorder," *J. Affective Disorders* 2007 (in press).

The Collins and McFarland paper is the only observational epidemiologic study cited by any of Plaintiffs' experts in support of their theory that Neurontin causes suicide. This study provides no evidence that Neurontin causes suicide or suicide attempt. This study did not attempt to perform a statistical comparison of suicide and suicide attempt rates in Neurontin-treated patients versus untreated subjects.

The manuscript by Collins and McFarland compared the risk of suicide and suicide attempts in a population of Medicaid patients with at least one diagnosis of bipolar disorder and at least one prescription claim for an anti-seizure medication. They reported that the relative hazard of suicide for neurontin compared to lithium was 2.6 and for suicide attempt the relative hazard was 1.6. The relative hazard for suicide was statistically significant and the relative hazard for suicide attempts was not significant. These were very similar to the relative hazards for the drug divalproex, with relative hazards of 1.5 and 2.7 for suicides and suicide attempts respectively, compared to lithium.

This is an observational epidemiological study in which the identified patients based on their exposure and then used medical claims data and death certificates to identify outcomes. There are a number of key limitations to this type of data for the study of drug effects, which may invalidate the study results. One of the most critical is that this is not a randomized controlled clinical trial. Therefore, the choice of medications may very well be linked to a higher risk of the outcome, in this case suicide and suicide attempts. In fact, the authors state "gabapentin is often prescribed for chronic pain which may well be related to suicide and suicide attempts."

Furthermore, the study was conducted because there was evidence that lithium was protective against suicide and suicide attempts, with numerous references to that literature in his manuscript. Dr. McFarland opined in his deposition that lithium has been shown to be protective against suicide and attempts, which was the premise of his study. (McFarland deposition, 60-61:17-3)

The study population is unique in that Medicaid is a program for indigent and disabled, and as such is unlikely to be representative of the general population. In particular, there are studies showing higher rates of mental illness in Medicaid. Groh, Poverty, Mental Health, and Women: Implications for Psychiatric Nurses in Primary Care Settings. J. Am. Psychiatric Nurses Assoc. 13(5):267-274 (2007). Also, adolescent suicide rates in Oregon are 39.6% higher than national suicide rates. MMWR, Fatal and nonfatal suicide

attempts among adolescents – Oregon, 1988 – 1993. 44:312 – 315 (1995) Therefore, it is not clear if these results would be valid outside of Oregon.

The reference drug used in the study was lithium, which is protective against suicide. Baldessarini, R.J., Pompili, M., Tondo, L., 2006. Suicide in bipolar disorder: risks and management. *CNS Spectr*. 11, 465–471; Baldessarini, R.J., Tondo, L., 2003. Suicide risk and treatments for patients with bipolar disorder. *JAMA* 290, 1517–1519. Because there was no untreated comparator, all the results can tell us is how these other drugs compared to lithium. They do not exclude the hypothesis that gabapentin protects against suicide and suicide attempt. McFarland agreed that it was not a valid, based on the results of his study, to conclude that patients taking gabapentin were at an increased risk of suicide compared to lithium. (McFarland deposition, 211:9-18) He did not intend the findings of his study to be misconstrued as indicating a risk of suicide with gabapentin. (McFarland deposition, 199:1-6;207:17-22)

C. Postmarketing surveillance

i. Parson's Report – September 9, 2004 Response to FDA Regarding Suicide and Suicide Attempt in Neurontin (gabapentin) Clinical Trials and Postmarketing Surveillance

The Parson's Report of September 2004 also summarized the adverse events reports accumulated within Pfizer's global postmarket adverse event database. By March 31, 2004 an estimated 12 million patients (worldwide) had been exposed to gabapentin and there were 17,768 adverse event (AE) reports in the company's adverse event database after excluding those from clinical studies (which were analyzed separately). . Response to FDA: Neurontin (September 9, 2004) Pfizer_MPatel_0039110. There were 35 case reports of completed suicides and 73 suicide attempts; 20 of these cases came from the literature via publications from poison control centers. *Id.* Suicides represented 0.2% of gabapentin reports. Published cases of suicide had limited or no information on critical factors that are associated with suicide risk including age, gender, reason for prescribing, other medications used, and medical history and as such were uninformative. In one case the cause of death was being questioned (homicide or suicide). Of the 10 suicides with supporting information, 8 reported risk factors for suicide and 2 contained limited information. *Id.* Suicide attempts represented 0.4% of gabapentin report. Fatal cases were reviewed for possible suicides and nonfatal cases reporting self-injury or suicide ideation were reviewed for possible suicide attempts. No additional completed suicides were identified and 4 additional cases of possible suicide attempt were identified.

Pfizer concluded that "a review of the available postmarketing data on gabapentin cases reporting suicide or suicide attempt does not support a causal association between gabapentin and suicide or suicide attempt. Pfizer will continue to monitor gabapentin cases reporting suicide and suicide attempt." *Id.* at 56.

I concur with the conclusions reached in this report. It is appropriate methodology to consider these results in context of the background rates of suicidal behavior in similar

populations. I disagree with Plaintiffs' expert, Cheryl Blume, that FDA "prohibits" such comparisons. (Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm -p.11).

ii. Mohan Report – "Gabapentin and Suicide" October 2005

This report describes the retrieval and evaluation of adverse event reports in the Pfizer in-house surveillance database. Pfizer, Inc., Response to EMEA, Appendix 4 (December 14, 2005). Gabapentin cases, through July 31, 2005, were searched for the MedDRA (ver. 8.0) preferred terms "completed suicide" and "suicide attempt." Additional preferred terms (self-injury, suicidal ideation, intentional self-injury, self-injurious behavior, self-mutilation, self-injurious ideation, suicidal ideation and depression suicidal) were all reviewed to identify any additional cases of suicide or suicide attempt. All fatal events were also reviewed to identify any that may have resulted from a suicide.

As of July 2005, there were 22,422 gabapentin non-clinical study cases in the Pfizer's safety database. Of these, there were 111 cases of suicide and 196 cases of suicide attempt. Of the 111 suicide cases, 38 had limited information on the exposure, other medication, and medical history; 30 were submitted as summonses by lawyers and 33 cases originated from the literature in Poison Control Center publications.

Pfizer concluded, "A review of the available postmarketing data on gabapentin cases reporting suicide or suicide attempt does not suggest a causal association between gabapentin and suicide or suicide attempt."

I concur with Pfizer's conclusions in this report. I also agree with Pfizer's statement that "[i]n post-marketing reports, analysis is confounded by polypharmacy, underlying psychiatric illness, negative dechallege/rechallege, and many case reports by lawsuits or contacts from plaintiffs' attorneys," and other factors. As demonstrated below, analysis of FDA's AERS database reveals the impact of stimulated reports from publicity and the activities associated with litigation. I agree with Pfizer's presentation of the limits of this type of data, particularly the effect of publicity on the reporting rates. I also agree with Pfizer that these data yield reporting rates, not incidence rates.

C. Regulatory action.

To my knowledge no regulatory agency has concluded that Neurontin is associated with an increased risk of suicidal behavior. As set forth below both FDA and the EMEA have specifically addressed this question and have not found such associations exist.

i.FDA

A citizen's petition was submitted by a law firm on May 17, 2004, alleging that Neurontin was causally linked to suicides among persons being treated with the medicine. Keith Altman, Finkelstein & Partners, Citizen Petition (May 17, 2004). The petition sought to require the manufacturer to "amplify" the Neurontin label regarding completed suicides for patients treated for "both its labeled and unlabeled indications." It is my understanding that this led to a series of analyses described above.

On March 21, 2005, the law firm submitted 258 MedWatch forms to FDA concerning patients who had committed suicide while on Neurontin. Letter from Andrew Finkelstein, Finkelstein & Partners, to FDA (March 21, 2005). As detailed below, these direct-to-FDA reports produced a significant reporting bias in the AERS database, such that one would not reach any reliable conclusion regarding a signal.

Despite the reports submitted by plaintiffs' attorneys, FDA has not concluded that Neurontin increases the risk for suicide or suicide attempt. It is important to note that, in its assessment of the law firm's petition, FDA noted that patients receiving treatment of Neurontin for psychiatric illnesses "are well known to be associated with an increased risk of suicide compared to the general population…[and]…in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any other factors that might explain these [suicide] events, such as concomitant medications." This letter reflects the common practice of comparing spontaneous adverse event reports to background rates, obtained from the peer-reviewed literature, in the appropriate patient populations. It also reflects the relative importance of randomized controlled clinical trial data in rendering judgments that a medicine is causally associated with a serious adverse event, such as suicide, which is common in the populations being treated with Neurontin.

ii. EMEA Report – January 2006

Broich and Lyonns. Joint response assessment report on list of outstanding issues Neurontine and associated tradenames (gabapentin) EMEA/H/A-30616. Report dates 01/12/2006-01/17/2006.

The EMEA, the European regulatory authority, conducted a detailed assessment on a number of outstanding issues regarding Neurontin. The report details the issues and the resulting discussion. In section I.3.1 Clinical aspects, Epilepsy, issues 8 (page 28), the agency asked for detailed data on the impact of a positive history of psychotic illness on the risk of psychotic or mood disorders, particularly the risk of suicide in patients treated with gabapentin. Based on their evaluation of the evidence, including the Mohan Report, discussed above, the assessor commented that there was "no clear evidence for a causal association between gabapentin and suicide or suicide attempt and show no causal association for a risk of psychotic or mood disorders in patients with a positive history of psychotic illness." Again, this judgment is based, in part, on consideration of postmarketing adverse event data in light of the occurrence of such events in the relevant populations.

Conclusion

Based on my evaluation of the clinical and epidemiological literature, and the pertinent Pfizer documents and regulatory submissions, I found no evidence of a positive statistical association between gabapentin and suicide or suicide attempt. The postmarketing analyses failed to detect a "signal" for suicide or suicide attempt. In addition, as Neurotin has been used in patient populations where there is a well-documented elevated risk of suicide compared to the general population, appropriate conclusions have been reached by Pfizer as to absence of an increased risk in the Neurontin-exposed populations.

Associations demonstrated in randomized clinical trials are generally accepted as providing the most reliable information for assessing whether a medicine causes an adverse event. The data from the Pfizer clinical trials provides no evidence of an association between Neurontin and suicide or suicide attempt. When considered with other study and postmarket data, and the collective assessment of regulatory agencies, the totality of the clinical and epidemiological evidence supports the null hypothesis - there is no association between Neurontin and suicide or suicide attempt. Given the total absence of any supportive data to establish an association between Neurontin and suicide or suicide attempt, it is entirely speculative and improper to assert as causal association between Neurontin and suicide or suicide attempt.

AERS Data Mining Analysis

I was asked to conduct an evaluation of the freedom of information act version of the FDA's spontaneous reporting system database (FOI-AERS) to determine if there was a statistical signal of suicide or suicide attempt with gabapentin. This analysis was conducted using QScan-FDA™ (Druglogic, Reston VA). Alsheikh-Ali, et al., The Safety of Rosuvastatin as Used in Common Clinical Practice: A Postmarketing Analysis. *Circulation* 111(23):3051-3057 (2005); Thompson, et al. Statin-Associated Myopathy. *JAMA* 289(13):1681-1690 (2003) These FOI-AERS reports were obtained by DrugLogic® (Reston, VA) and then subjected to a variety of proprietary steps to clean the data and link it with corresponding dictionaries for drug names, ingredients, and adverse event terminology (MedDRA). I routinely use this database in my pharmacovigilence activities, teaching and research. If there were initial and follow-up reports of the same case, only the most complete report was counted. There may be unapparent duplicate cases, particularly if they were reported by different sources.

In the FOI-AERS database there were 30,528 adverse event cases where the drug gabapentin was mentioned by the reporter as the suspect drug (i.e., suspected by the reporter of the event as the drug involved with the adverse event) or a concomitant drug. More than 50% of cases were reported after 2003, 10 years after Neurontin was approved. The number of spontaneous reports for gabapentin appears to have peaked in 2005.

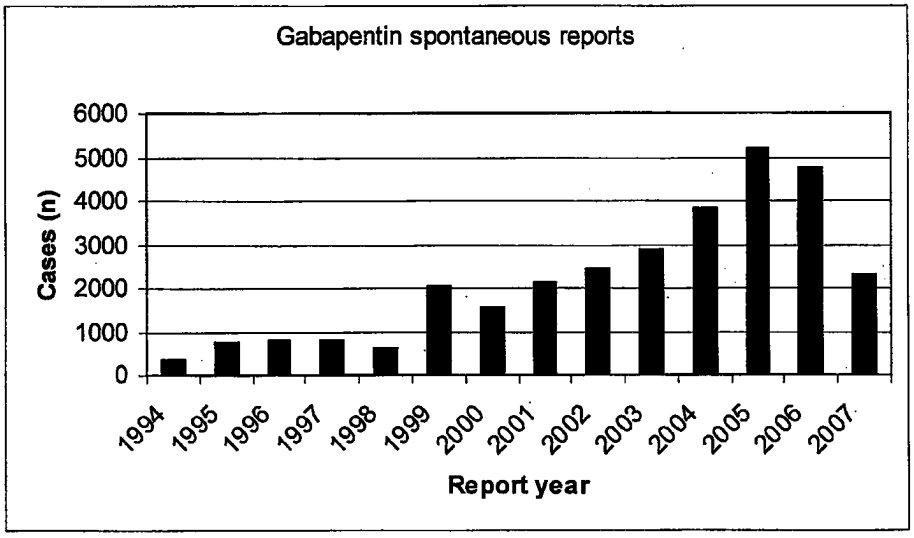


Figure 1. FDA spontaneous reports with gabapentin listed as suspect or concomitant medication by year of report, FOI-AERS 1994-2007.

Prescription sales data are necessary to put the adverse event reporting trend into perspective in that it provides an estimate of patient exposure and how it changes over time. (CITE CDER 2005 PV). As shown in Figure 2, Neurontin was widely marketed and used in more than 12 million patients (per Parsons report) by 2005. Prescriptions for the gabapentin (brand and generic) have increased over time from 243,528 prescriptions in 1993 to an estimated 16.7 million in 2006. In 2005 alone, 16.7 million total prescriptions were written for gabapentin (brand plus generic) according to Verispan and 19.8 million according to IMS.

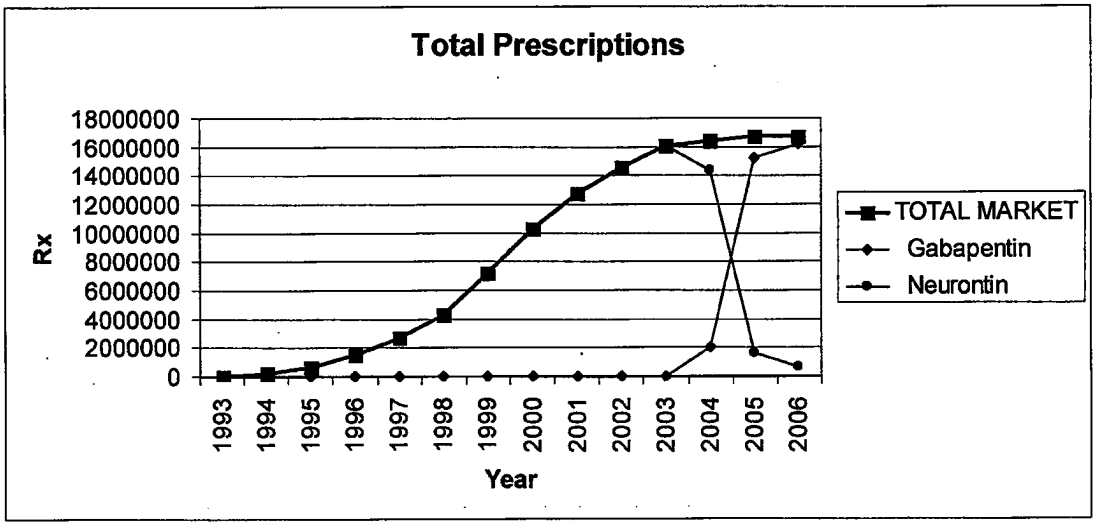


Figure 2. Total prescriptions for the brand name (Neurontin) and the generic version of gabapentin in the United States, 1993-2006 (*source Verispan)

As shown below in Figure 3, as the total prescriptions increased to over 16 million per year from 2003 onward, the proportion of adverse events in relation to sales dropped to 0.018% in 2003. As patient exposure to Neurontin increased over time, the proportion of adverse events relative to this exposure declined. This provides evidence against the assertion that the increases in adverse event reports over time constitute a "signal" of any kind, but is instead indicative of what is expected with a widely used medication.

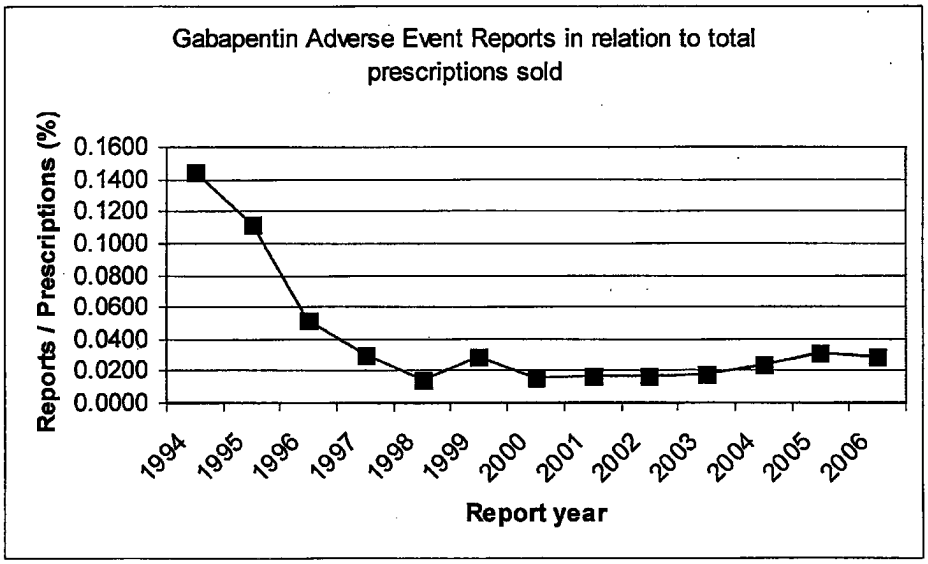


Figure 3. Annual adverse event reports (total) for gabapentin as a proportion of the total prescription sales in that year, FOI-AERS (adverse events) and Verispan (total prescriptions)

In the FOI-AERS database, we repeated the search to cases in which gabapentin was noted by the reporter as the "suspect" drug, regardless of whether there were any additional suspect and/or concomitant medications listed. The proportion of total cases in which gabapentin was selected as the suspect drug was highest in the first three years of marketing and then tapered off rapidly. It stayed at less than 50% since 2001. (Figure 4)

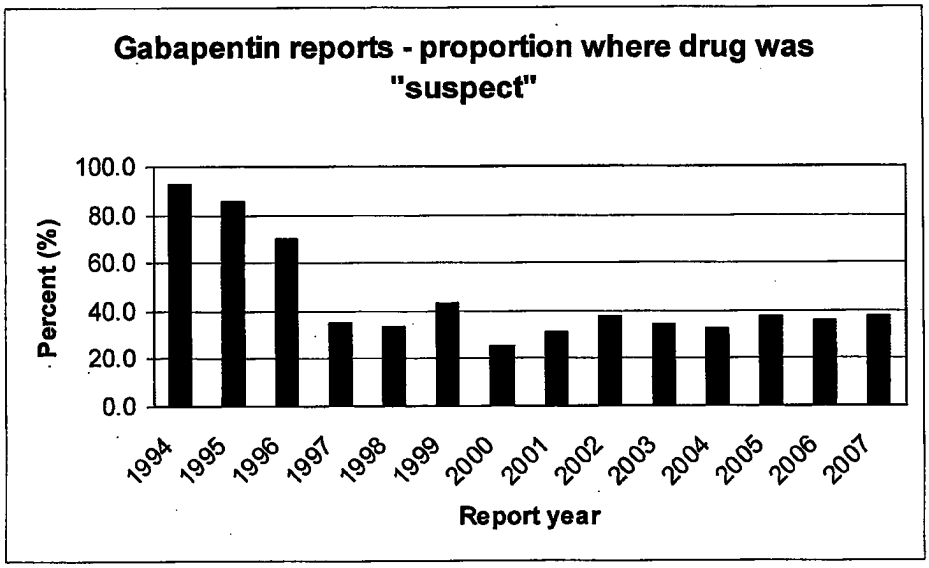


Figure 4. Annual percentage of gabapentin total reports where the reporter identified gabapentin as a suspect agent, FOI-AERS 1994-2007

While the pattern in Figure 4 (above) is not remarkable, looking at the same group of reports (gabapentin as suspect drug) by the type of report provides a very different picture. Reports are characterized into three types by the how they are received and the speed of reporting. Direct reports are those which are sent directly to the FDA by the reporter (e.g. consumer, physician, lawyer) through the MedWatch Program (www.fda.gov/medwatch). Expedited and periodic reports are sent to the FDA through the manufacturer, with expedited (or 15-day reports) being serious and unexpected events which must be reported within 15-days of the manufacturer becoming aware of the event. (21 C.F.R. §314.80). As shown below in Figure 5, in each year from 1999 through 2006, the total number of gabapentin reports increased, with a peak in 2005. This is consistent with the increased use of gabapentin, as well as an overall increase in adverse event reporting to FDA for all drugs. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm. What is remarkable is a dramatic jump in the number of direct reports in the year 2005. From 1994 – 2004, the number of direct reports increased from 28 to 130. From 2004 – 2005, the number of direct reports jumped to 595 reports. Thus, in just one year, the number of direct reports increased as much as it had over the previous 10 years (358% increase in one year).

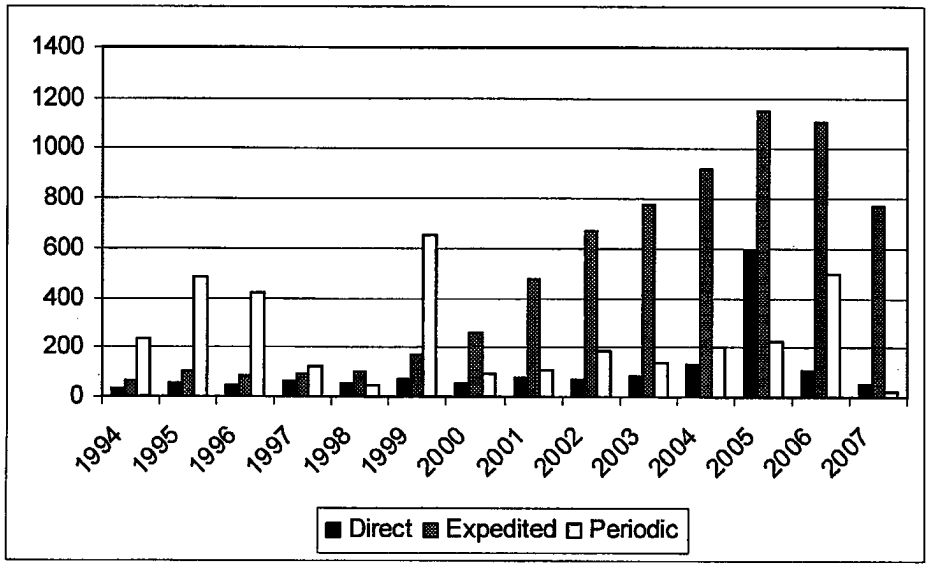


Figure 6. Number of reports in which gabapentin was indicated as the suspect drug annually, by report type, 1994-2007.

To further explore why there was a sudden and dramatic increase in direct reports in 2005, with gabapentin as the suspect agent I looked at the distribution of reports each quarter (based on report date) by the patient outcome. These are the outcomes which are checkboxes in the Medwatch form. As shown below in figure 7, there is a very large number of deaths reported (n=315) in the first quarter of 2005. Over the entire time of marketing, the overall proportion of deaths was less than five percent, but in the first quarter of 2005, this was 20%.

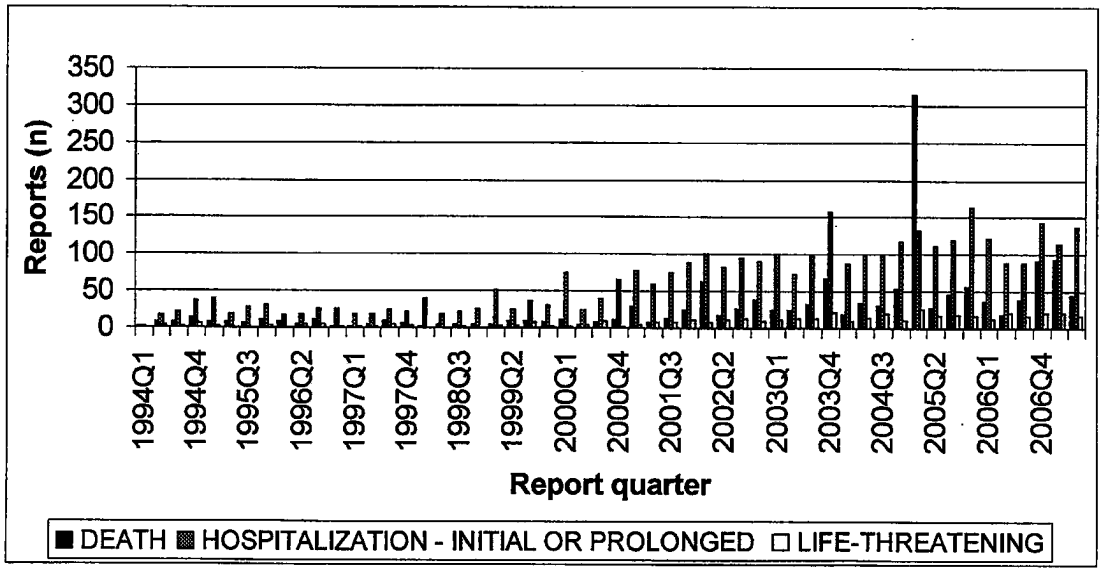


Figure 7. Number of reports in which gabapentin was indicated as the suspect drug quarterly, by report type, 1994-2007.

Again looking at cases where gapapentin reported as "suspect", but this time by the event date, the peak seen in the above figures disappears (Figure 8). This demonstrates that the first quarter 2005 peak in reports, shown in the figures above were caused by stimulated reporting. Of the deaths reported in the first quarter of 2005, 88.3% were suicides, and 83.5% were reported directly (i.e., not from a manufacturer) to FDA. In fact, most the reports (82.9%) were submitted to FDA during just 4 days at the end of March of 2005. These direct reports severely undermine the utility of the FDA FOI-AERS for signal detection. Analysis of this data is based on disproportionality in reporting rates. Once there is stimulated reporting, data mining is no longer valid.

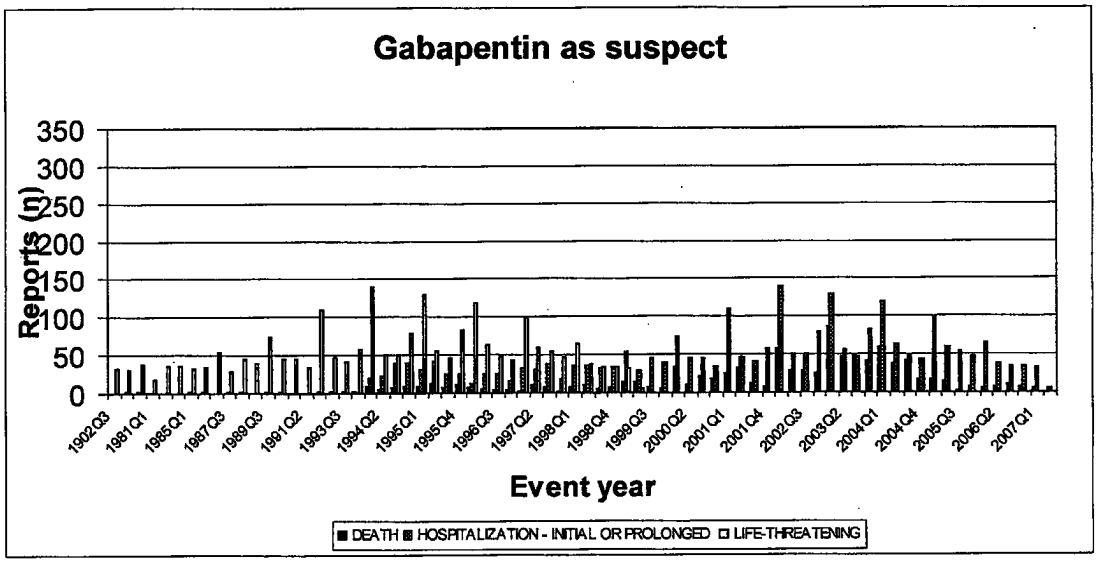


Figure 8. Number of reports in which gabapentin was indicated as the suspect drug by the event date (quarterly) and report type, 1994-2007.

Data mining is the use of statistical algorithms to quickly process large databases of adverse events and identify otherwise unexpected relationships between a drug and an adverse event (drug-event pairs) or a drug-drug interactions (drug-drug-event). It differs from a scientific study, in that data mining is purely exploratory, while scientific studies are designed to test one or more predefined hypotheses. Drug-event pairs are identified by data mining as being statistically linked, such that they are more commonly found together in the database then would be expected compared to a specified background. To differentiate data mining results from a clinical specialist evaluating a series of adverse event reports and generating a hypothesis of potential causality (typically called a "signal"), the terms "alerts" or "signals of disproportional reporting" (SDR) are used. An alert or SDRs is purely a statistical association. It may or may not be clinically meaningful, and "…true signals should emerge from clinical judgment and that statistical algorithms, such as PRRs, should be used as supplements to clinical and epidemiological judgment, not replacements." Strom, Evaluation of suspected adverse drug reactions. *JAMA* 293:1324 – 1325 (2005).

Using the full dataset as the background, I calculated a cumulative series of Proportional Reporting Rates (PRR). Hauben and Zhou, Quantitative Methods in Pharmacovigilance: Focus on Signal Detection. Drug Safety 26:159 – 186 (2003). The threshold of a PRR greater than 2 with a Chi-squared ≥ 4 and an N>2 are commonly cited as the criteria for a statistically significant alert. Hauben M, et al., Data mining in pharmacovigilance: the need for a balanced perspective. *Drug Safety* 2005; 28(10):835-842; Evans, et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Safety* 2001; 10:483-486; Kubota, et al. Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiology & Drug Safety* 13(6):387-94, 2004; Almenoff, et al. Comparative performance of two quantitative safety signalling methods: implications for use in a pharmacovigilance department. *Drug Safety* 2006; 29(10):875-887. PRR was chosen as it is the most inclusive algorithm. Using these criteria, neither of these terms reached the significance threshold until 2005 (Figure 9). This is the year where there was a significant rise in stimulated reports. Therefore, the signal can almost certainly be attributed to bias in reporting of suicides and suicide attempts that was seen in the first quarter of 2005.

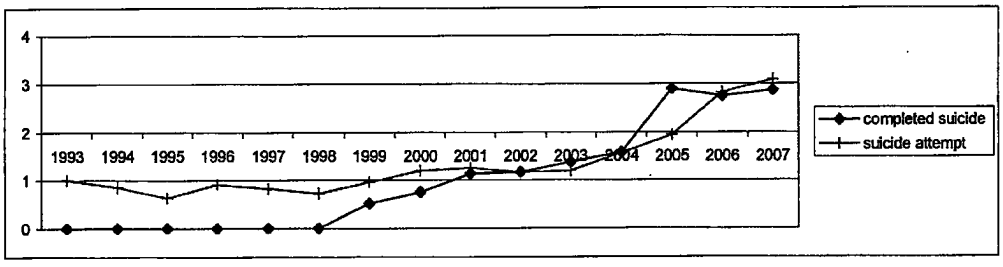


Figure 9. Proportional reporting rate values when comparing the proportion of reports for gabapentin that had the preferred terms "completed suicide" and/or "suicide attempt"

compared to the frequency of these terms in the AERS database (background rate), FOI-AERS 1993-2007.

Looking at the same analysis in a different way, using the threshold of PPR>2, Chi-squared ≥ 4, and n>2, the results are the same. The figure below notes when these criteria are met (0=not met, 1=criteria met). Again, as in the plot above, it is clear that there is no data mining alert for suicide with gabapentin (this includes all reports, whether it was suspect or concomitant). Based on the Figure 10 (reports listing only gab – case counts x quarter), it is almost certain that the PPR met the above criteria as a result of the 258 direct reports submitted in first Quarter 2005 (as noted in the letter from Dr. Katz to Mr. Finkelstein).

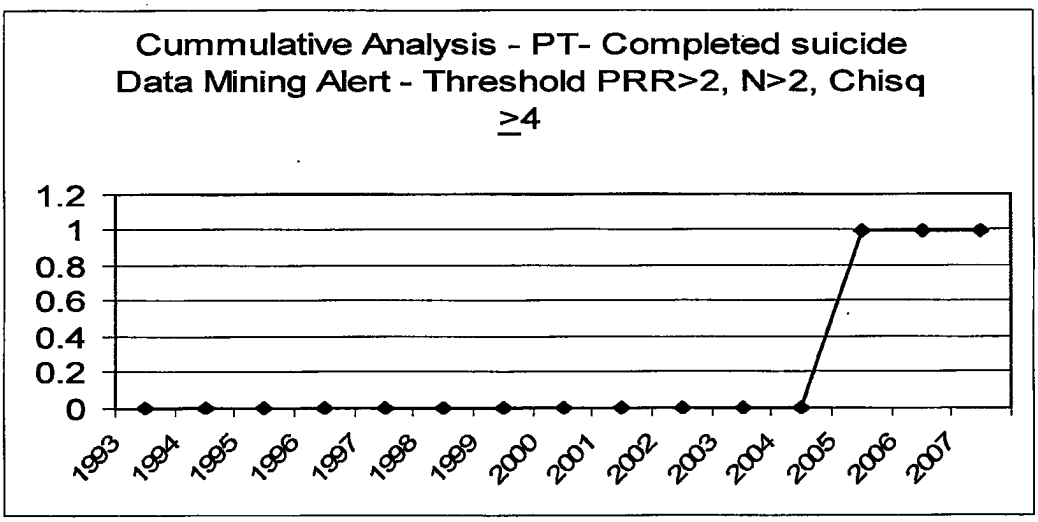


Figure 10. Identifying the initial date of a statistical alert with gabapentin based on a comparison of proportional reporting of suicide against the background of all reports, FOI-AERS, 1993-2007.

Any assertion of signal between Neurontin and suicide is not supported by my statistical evaluation (data mining) of FOI-AERS reports. The analysis presented here reveals a pattern of reporting that is not consistent with a pharmacological affect of a medicine. To the contrary there is evidence of significant bias in the reporting of suicides to the FDA's adverse event database which can be attributed to the plaintiff's attorneys. Letter from Dr. Russell Katz, Director, FDA Division of Neuropharmacology, to Andrew Finkelstein (April 12, 2005) This dumping of suicide reports is clearly evident in the first quarter of 2005. As Dr. Blume testified at her deposition, notoriety bias would impact postmarketing surveillance as early as 2003. This renders any evaluation of proportional reporting rates (eg. data mining) to detect alerts or signals of disproportional reporting (SDRs) during this time period meaningless.

Critique of the reports from the plaintiff's experts

A. Dr. Sander Greenland's report – October 19, 2007

Dr. Greenland does not practice in the subspecialty of pharmacoepidemiology. His central premise is that the wealth of information from randomized controlled clinical trials, uncontrolled clinical trials, epidemiologic literature, and postmarketing surveillance does not permit any scientific conclusion on the question of whether Neurontin causes suicide. Dr. Greenland ignores a substantial body of consistent evidence that are routinely utilized in pharmacoepidemiology to make important drug safety decisions, including whether an agent is causally associated with an adverse event. The totality of the data supports the conclusion that Neurontin is not associated with an increase risk of suicide or suicide attempt. Nowhere in his analysis does Dr. Greenland conclude that Neurontin is associated with or causes suicide, suicide attempt, or suicidal behavior.

Specifically, Dr. Greenland states that the June 2006 from Mary Ann Colonel Evertsz, R,Ph. to Dr. Russell G. Katz, division director, Division of Neurology Products, CDER, FDA "provide no evidence regarding a presence or absence of a relation of gabapentin to suicide because there were no suicides and only one suicide attempt among more than 50 randomized, placebo-controlled clinical trials." Greenland Report at p. 2 Among the studies which met FDA inclusion criteria there were 8829 subjects (including patients and volunteers); 5194 treated with Neurontin. This was after extensive case finding, in which all death reports and all potential suicide attempts were blindly reviewed by qualified Pfizer physicians to identify any possible suicides. This used a methodology developed by Dr. Posner at Columbia University for the study of suicides with antidepressant use. Pfizer's conclusion that Neurontin neither causes nor was associated with an increased risk of suicidal behavior is solidly based on the accumulated evidence. Given that the clinical trial patients are at increased risk of suicide by virtue of the conditions for which they were enrolled in the clinical trials (e.g. epilepsy, chronic pain) and that there were no suicides among these patients is indeed supportive of the null hypothesis. There is no evidence of an increased risk .

Dr. Greenland states that "the data are statistically compatible with any and every hypothesis about the gabapentin effect." There are always three possible hypotheses, positive, negative, and neutral or null. He consistently at numerous points throughout his report, provides only two of the three possible hypotheses; the first being the null or no effect and a second being a negative effect (increased risk). However, he continually fails to note the third plausible hypothesis which the statistical trial data are also compatible with the hypothesis that gabapentin is protective against suicide. While each individual study – all which were consistent with the null hypotheses (no effect) – does not provide definitive evidence by itself, the totality of the evidence supports the conclusion that Neurontin is not associated with an increased risk of suicide.

On Page 9, Dr. Greenland states in a discussion of adverse event reports, that "case-report databases at best provide a sentinel alert for adverse events associated with a drug..." This is indeed true, despite the misuse and misinterpretation of such data in the Blume report. When appropriate analyses of postmarketing data are conducted it is clear that no signal of suicidality emerged at any time prior to 2005. It is not disputed in this case, that after 2003 the effects of publicity and other factors biased reporting such that it totally negated the value of this database for any signaling. My opinions and analysis on this issue are provided above.

Dr. Greenland criticizes Pfizer's assessment of adverse event reports by noting that the elimination of cases based on a clinical assessment "is a violation of standard protocol in randomized clinical trials, which proscribe exclusions following randomization (Greenland et al, 2008)" (page 9) In a clinical trial, patients are randomization into treatment or comparator (placebo) arms and the frequency of events can be compared between the arms. In spontaneous reports there are only events; no randomization and no comparator arm(s). Therefore, reports are evaluated differently and for a different purpose. It is standard practice in pharmacovigilance to evaluate each report individually to see if there are reports in which there is no plausible alternative for the event, except for the drug. Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) March 2005. http://www.fda.gov/cder/guidance/6359OCC.htm; Strom, 4th ed., Chap. 36, p. 557.

On Page 10, Dr. Greenland states: "Elimination of cases in this fashion leads to underestimation of suicide rates in postmarketing surveillance and uncontrolled comparisons, which greatly increases the likelihood of false-negative results (failure to find a genuine excess)." This is misleading as the rates of suicide or of any other condition cannot be determined from spontaneous reports. As spontaneous reports are voluntary, only an unknown proportion of all events are reported to the FDA or the manufacturer. The denominator is also unknown and can only be roughly estimated from national sales or prescription data.

On Page 11, Dr. Greenland suggests that the validity of the postmarketing data can be assessed by taking the ratio of attempted to completed suicides, and gives a ratio of 2.1 and compares it to the 6.0 from the clinical trials (Parsons report) and 7.2 from an observation study (Collins & McFarland Paper). A low ratio of suicides to suicide attempts is expected in spontaneous reporting data, as seriousness of the outcome is one of the criteria for reporting. Suicide attempts that do not meet the criteria for a serious adverse event (21 C.F.R. § 314.80) may not be reported to the FDA as individual reports. My independent academic research has shown that starting in1998, immediately following the initiation of AERS, the number reports released in the FIO-AERS database was only half of the number of reports as received by CDER.

B. Cheryl Blume's report

Based on her CV, report, and deposition it is clear that Dr. Blume has little or no training in epidemiology and is not an epidemiologist or a pharmacoepidemiologist. Specific examples are listed below. Her CV is devoid of any mention of expertise, training, or publications in epidemiology or pharmacoepidemiology. She is listed as a member, but not a fellow, of the International Society of Pharmacoepidemiology (ISPE) as of October 2007. The only requirement for general membership is payment of the $220 dues. I searched the abstracts, poster sessions, and listings of podium presentations and could find no evidence of her participated in any way at any of ISPE's annual meetings over the last five years. Similarly, she has not been listed as an author or co-author in any manuscript published in the official journal of the society, Pharmacoepidemiology & Drug Safety.

In discussing the clinical trial data, Dr. Blume states that the clinical development "....include studies designed to assess the clinical safety and efficacy of a drug in the patient population for whom the drug *will be prescribed.*" This is incorrect. The studies must be conducting in patients for whom the drug *will be indicated*, that is the intended population as it is written in the drug label and for which the drug will be approved. The indicated disease or condition is chosen by the drug sponsor/manufacturer and not the FDA. Once a drug is on the market it can be prescribed by physicians differently from how it is labeled. This "off-label prescribing" is quite common, particularly for children and in the field of psychiatry. Radley, D., et al. Off-label Prescribing Among Office-Based Physicians. *Arch Int Med.* 2006; 166:1021-26; Barbui, C., et al. Off-label and non-classical prescriptions of antipsychotic agents in ordinary in-patient practice. *Acta Psychiatr Scand* 2004; 109:275-78; Chen, H., et al. An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid Population. *Pharmacoepidemiology & Drug Safety* 2005; 14:629-38. In a study of off –label prescribing among Georgia Medicaid recipients, Chen et al found that more than 70% of patients receiving anti-convulsants were prescribed the drugs for off-label uses. The rates of off-label prescribing were highest among the newer anti-convulsants and being younger than 18 years, was a significant predictor of off-label use. Hua, et al., An epidemiological investigation of off-label anticonvulsantdrug use in the Georgia Medicaid population. *Pharmacoepidemiology and Drug Safety* 2005; 14: 629-638.

Paragraph 31. On postmarketing reports, Dr. Blume states "The system also detects increases in the frequency or severity of previously identified events." This is incorrect. The rate of events (i.e. frequency) among those at risk (i.e. exposed) cannot be determined from such reports as the numerator (total events that occurred) and the denominator (persons at risk) are both unknown. Therefore, changes in the frequency of events cannot be calculated from reports.

Paragraph 46. Dr. Blume contends, at several points in her report, that Neurontin causes or exacerbates depression and anxiety is contradicted by the results of three well-controlled randomized clinical trials specifically studying Neurontin in patients with various psychiatric disorders. . In all three of these trials -- involving patients with panic

disorder, bipolar disorder, and social phobia -- researchers utilized Hamilton Depression (or HAM-D) and Hamilton Anxiety (HAM-A) Scales to evaluate depression and anxiety, respectively. Research Report 720-04174 (March 26, 1999) (bipolar controlled study); Research Report 720-03851 (April 9, 1999) (panic disorder study); Research Report 720-03850 (March 19, 1999) (social phobia study). Results from all three studies showed no worsening in either the HAM-D or HAM-A scores at any time during the study period, indicating no emergence or exacerbation of depression or anxiety. There were no reports of suicide or attempted suicide by a patient on gabapentin in any of the three psychiatric clinical studies. And although there were reports of suicidal ideation by patients on placebo in the psychiatric controlled studies, there were no such reports in any patients on gabapentin. It is my opinion that the data from the bipolar, social phobia, and panic disorder controlled studies supports the hypothesis that Neurontin does not cause or worsen depression or anxiety.

Paragraphs 52-56. Dr. Blume provides some background information on the concepts of dechallenge and rechallenge and asserts that there were "Incidences of positive dechallenge/rechallenge events have been documented in clinical trials involving gabapentin" and specifically notes the events as suicidal ideation, depression and hostility. In certain limited contexts, an event that goes away when a drug is withdrawn and then comes back again when the drug is reintroduced, can provide support of a causal association. However, a temporally-related sequence of events is not always evidence of dechallenge – rechallenge – and as such does not prove causality. The hazard of falsely presuming that cycling of symptoms is evidence of a positive rechallenge is well described by Girard (Girard, Conclusiveness of rechallenge in the interpretation of adverse drug reactions. *Br J Clin Pharmacol.* 23:73 - 79 (1987)). *See, also* Vilhjalmsson, et al., Factors associated with suicide ideation in adults. Soc. Psychiatry Psych. Epidemiol. 33:97 – 103 (1998). Particular to depression, FDA scientists Drs. O'Connell, Wilkin, and Pitts write that "Reports that document positive rechallence do not prove a causal relationship for events such as depression that have a high background rate and a chronic remitting natural history." Vilhjalmsson, et al., Factors associated with suicide ideation in adults. *Soc. Psychiatry Psych. Epidemiol.* 33:97 – 103 (1998) Given the use of gabapentin in populations that have a high rates of depression (e.g. epilepsy and chronic pain) as well as a disease which manifests with episodes of depression (i.e. bipolar disorder) resolution and the subsequent reoccurrence of depression or depressive symptoms that are temporally related to treatment do not provide evidence for causality. Depression is a subjective measure (qualitative) – and not measured in a valid way in event reports. Given high background and lack of specificity, cycling of depressive symptoms is not considered evidence of positive dechallenge/rechallenge.

Paragraph 59. Dr. Blume states that "suicide related events associated with Neurontin were evidence in the clinical trial data." This statement is at odds with the clinical trial data as summarized by Evertsz in which there were no suicides and only one suicide attempt in all of the randomized controlled trials. Response to FDA Suicidality Request (June 22, 2006), Pfizer_MEvertsz_0079431

Paragraphs 60-92. In this section, and in other sections throughout her report, Dr. Blume present tables which list terms, which she calls "psychobiological adverse events," and numbers. Data in such tables are uninterruptible and of no scientific value. A critical limitation is the absence of any methodology for her independent review of the clinical studies and postmarketing event reports and their compilation into tables. In particular, she provides neither a definition of the term "psychobiological adverse events" nor any references to this concept in the medical literature. Its validity as a measure of suicide-related events is unproven. Thus, it is scientifically inappropriate to attempt to show a causal relationship between Neurontin and suicide or suicide attempt based on purported changes of these "psychobiological adverse events." She provides no information on her methods; how the events were abstracted and clinically adjudicated or how she dealt with multiple terms together in a single case. Given the subjective nature of these events, a standardized protocol is necessary to find cases, followed by a standardized and critical evaluate narratives by an experienced clinician (ideally blinded to exposure), as was the protocol followed in Pfizer in their evaluation of the clinical and postmarketing data (*REF the Evertsz report, Parsons.) Furthermore, her tables are filled with raw counts (the number of purported events) and as such are uninterruptible. Without calculating and statistically comparing rates or proportions, these tables are essentially meaningless and inferences cannot be drawn from them.

Paragraph 96. Dr. Blume gives the proportion of patients who withdrew from trials by their treatment (gabapentin and placebo) and states that among patients who withdrew from these studies, the proportion that withdrew due to "clinically related psychobiologic events" was greater among gabapentin-exposed than among placebo-exposed. In addition to the dubious validity of her methodology, she also provides no statistical analysis to support this statement. There is no context to determine if the proportions provided are statistically different or due to random error.

Paragraph 101. Dr. Blume states that surveillance data provides "signals of increased numbers of deaths, suicide attempts, overdose, etc.", during the period 1994-1996. She makes similar statements throughout her report, in which she incorrectly calls the accumulation of adverse event reports over time *trends*, and that such "trends" are *signals*. Statistically, three years of data are not adequate to establish trends over time. Additionally, as long as a drug is marketed (and for a period following withdrawal), the number of reports that mention the drug will continue to accumulate. As Neurontin was approved in December 1993, it is expected that adverse events would accumulate in the FDA database. An accumulation of event reports do not constitute a "signal."

Paragraph 119. In her review of the World Health Organization's adverse event database, Dr. Blume states "The *incidence* of reports of psychiatric disorders (psychiatric disorder-related reports / total reports) during 1994-1996 was 22% (87/395) in 1994; 18% (201/1116) in 1995; and 16% (82/514) in 1996." However, the proportions presented are *not incidence*, which is one of the first measures of disease frequency that is taught in introductory epidemiology courses. Incidence is calculated by dividing the number of new events by the total persons at risk (or person-time at risk). What she gives here are actually proportions based on case reports and as such cannot be interpreted as incidence rates.

Paragraph 167. Her definition of nonserious events is unusual and contrary to the regulatory definition. In her report Dr. Blume writes "Pfizer Defendants' discussion of overdose events emphasized the *non-serious cases* (*i.e.*, those where the event was attributed to another drug or there was no report of a daily dose in excess of the label recommendation). Based on 21 C.F.R. § 314,80, a serious adverse event is defined as "Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." A non-serious adverse event is an event that does not rise to the level of a serious event. Dr. Blume's definition is inconsistent with this definition.

Paragraph 175 – Dr. Blume notes "...increases were also observed in the SRS/AERS database for the numbers of aggression, anxiety, agitation, depersonalization and depression events from 1996 to 2002." It is also important to put these into context which takes into account the increases in gabapentin sales, increases in total adverse event reports for gabapentin, and increases in adverse event reporting for all drugs during this time period. Another change that is likely to cause a spurious increase in nonserious (and perhaps nonspecific) adverse event terms was the change from SRS to AERS in late 1997. That transition was accompanied by a change in the medical dictionary for adverse event terminology, from COSTART to MedDRA, and an increase in the number of terms that could be recorded, from four (COSTART) to unlimited (MedDRA), per report. Neal, *et al.*, MedDRA and pharmacovigilance - the way forward. DIA annual meeting. June 27-July 1 1999.
Slide # 7, http://www.fda.gov/cder/present/dia-699/dia628/sld007.htm

Paragraph 234. Dr. Blume criticizes the protocol used to identify possible suicide-related events, which was established by the FDA scientists in conjunction with Dr. Posner, Columbia University, as "arguably too narrow to appropriately reflect all psychobiologic adverse events including suicidal events." Indeed that is exactly why the FDA would insist that companies follow their established and tested protocol. Creating a clear and valid case definition and a reproducible (reliable) protocol to guide an unbiased identification of cases, and exclusion of non-cases, is a necessary step in any epidemiological study. A case definition that is too broad such that it incorporates a heterogeneous constellation of conditions (e.g. psychobiological events) would tend to bias a study toward the null hypothesis, finding no association when one exists. Strom, 4th Ed., Chapt. 8, p. 118.

Paragraph 244. Dr. Blume states that "Pfizer Defendants should have recognized the growing numbers of .... completed suicides that continued to accumulate in their internal

database" and notes the increases in suicides from 2002-2004 period. Not only does she neglect to mention that were no (zero) completed suicides reported for the first five years of marketing, but these raw numbers are taken out of context. Using the FOI-AERS database, and prescription sales data from Verispan, I plotted the number of completed suicides reported and the number of adverse event reports which mentioned gabapentin by report year alongside the total prescriptions. During the same period, there were substantial increases in the total number of gabapentin adverse event reports each year and also substantial growth in total prescription sales. (See Figure 11). Again, the large increase in the number of suicide reports in 2004 and 2005 is likely the result of increased direct-to-FDA reporting related to litigation and publicity.

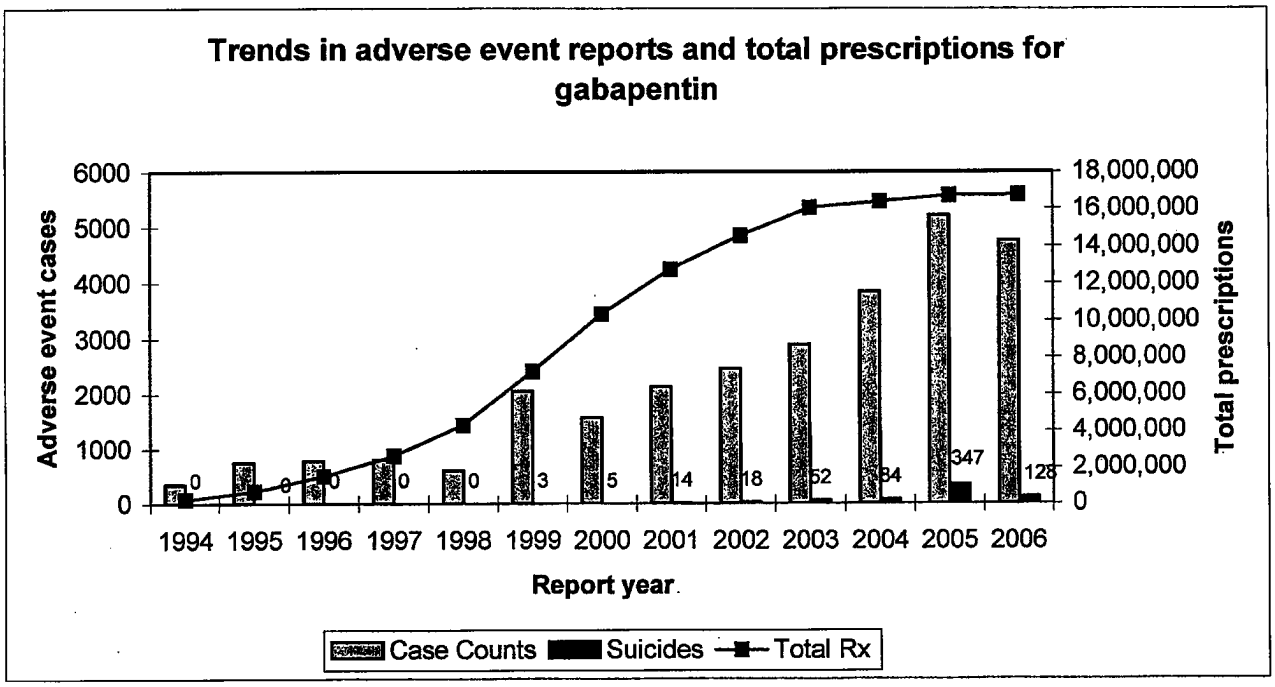


Figure 11. Trends in gabapentin prescription sales and adverse event reports over time.

Paragraph 245. Dr. Blume criticizes Pfizer's scientists for putting suicide reports into context by considering the background rate of suicide in the patient populations who are likely receiving gabapentin and the total adverse events reported by saying 'these rationalizations have been previously criticized by FDA as inadequate and not applicable for suicide-related events" and quoting an FDA alert to health professionals: Isotretinoin (marked as Accutane), FDA; November 2005 http://www.fda.gov/cder/drug/InfoSheets/HCP/IsotretinoinHCP.htm. Her criticisms are misplaced. First, I find nothing in the referenced FDA alert that addresses the issue at hand and second, the FDA clearly states in their Guidance to Industry on Good Pharmacovigilance Practices (REF March 2005, Section G. Page 10), that reports of an event should be considered in the context of exposures (specifically mentioning prescription sales) and the background rates of the event in the population "ideally, in a subpopulation with characteristics similar to that of the exposed population."

Paragraph 248. Dr. Blume notes "by the end of 2005, completed suicide comprised over 3% of the total database." Because of the stimulated reporting of reports of suicide with Neurontin (primarily because of events reported directly to FDA by a law firm), which is readily apparent in the first quarter of 2005. In her deposition, Dr. Blume conceded that such notoriety bias likely began two years before. Completed suicide reports have been increasing in AERS, regardless of medication. This needs to be taken within the context of the overall increase in all AERS reports (CDER 2005 Report to the Nation) and the real increase in suicides rates among young America's from 2003-2004. Lubell, *et al.* Suicide Trends Among Youths and Young Adults Aged 10--24 Years --- United States, 1990—2004. MMWR. September 7, 2007 / 56(35);905-908, at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5635a2.htm

Dr. Blume makes numerous misstatements about data mining and particularly, the Proportional Reporting Ratio (PRR) in her paragraphs 313-320, some of these are highlighted in below.

Paragraph 313. She states that PRRs can be used to "compare different adverse events within a product or differences in adverse events between two products." When properly conducted, a PRR is a calculation of whether a particular drug-event combination is reported more often together than expected. It does this by "generating a score by comparing the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with the fraction of reports for the same particular event for all drugs (i.e.,"the expected reporting fraction"). FDA Guidance document – pharmacovigilance, page 8. This score is then statically evaluated in context of a predetermined threshold. Importantly, at her deposition, Dr. Blume denied using any statistical methods to "compare different adverse events."

Paragraph 314. In her discussion of data mining, and particularly the PRR, Dr. Blume purports "a signal is considered whenever the PRR exceeds one." A review of the literature of data mining studies shows a threshold of a PRR of two or greater is commonly used in conjunction with a Chi-squared ≥ 4, and an $n \geq 3$. Hauben M, et al., Data mining in pharmacovigilance: the need for a balanced perspective. *Drug Safety* 2005; 28(10):835-842; Evans, et al. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Safety* 2001; 10:483-486; Kubota, et al. Comparison of data mining methodologies using Japanese spontaneous reports. *Pharmacoepidemiology & Drug Safety* 13(6):387-94, 2004; Almenoff, et al. Comparative performance of two quantitative safety signalling methods: implications for use in a pharmacovigilance department. *Drug Safety* 2006; 29(10):875-887.

Paragraph 320. Dr. Blume makes reference to a chart in her report, that it "reflecting the PRR for Suicidal and Self-Injurious Behavior." However, there are no PRR values in the referenced chart (page 194). Because PRR is a ratio of two proportions, the resulting value has no units. In her chart, the y-axis is labeled % reports. It appears that this is just the percentage of total reports (for each of the drugs) that had a coded event that fell

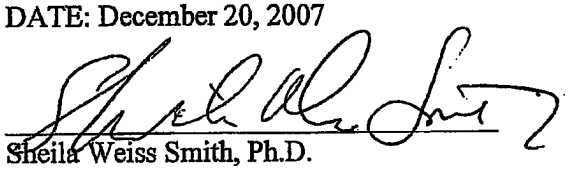
within the broader higher level term "SUICIDAL AND SELF-INJURIOUS BEHAVIOUR".

Paragraph 323. Dr. Blume references a chart that she created based on data from what appears to be a consultation report (dated Feb 6, 2007) from Drs. Gelperin and Green to Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products. She neglects that the authors noted "in a passive surveillance database such as AERS and as stated in a previous consult dated July 16, 2002,66 it is difficult to discern the drug effect associated with reported cardiac events in a non-randomized controlled trial setting." It is misleading to state that this is what the FDA based their determination of a signal for Avandia. The bulk of the briefing document deals with randomized controlled clinical trials and meta-analyses of these trials. In his presentation slides at that same meeting, Dr. David Graham, the senior medical epidemiologist, presented the clinical trial data to the total exclusion of AERS reports. http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-00-index.htm. The plot that she referenced was in an internal FDA consultation, that was part of the briefing document provided to advisory committee members prior to the meeting. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf. I could find no evidence that these data were discussed or presented during the advisory committee meeting, nor considered by the members in their review. http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-00-index.htm) In fact, they discussed the limitations of "high quality and well conducted" observational studies in informing their decision because of biases. http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4308m1-final.pdf - page 5) Adverse event reporting rates, which are what Dr. Blume presents here, are even less informative as they are not research studies at all and are subject to all of the well known and described limitations of postmarketing surveillance. Strom, 4th Ed., Chapt. 9, p. 152 – 154. There is no support for her statement that FDA has approved her methodology of analyzing the AERS database. Furthermore, the use of single comparator drugs, as presented in Dr. Blume's report (page 194), is improper, and there is no valid analysis to assert that the percentages that she presents are statistically different.

In summary

The totality of the clinical trial, observational studies, and postmarketing data fails to establish an association between gabapentin and suicide or suicide attempt. There were no suicides in the randomized clinical trials. Data mining of the spontaneous reporting system did not identify a statistically significant alert or signal of disproportional reporting for the preferred terms "suicide" or "suicide attempt" until 2005. That same year, in the first quarter of 2005, there is clear evidence of stimulated reporting by the plaintiff's attorneys themselves. Neither FDA nor any other regulatory agency has found that Neurontin is associated with suicide or suicide attempt. No medical or scientific peer-reviewed literature has established that Neurontin is associated with or causes suicide or suicide attempt. With reasonable scientific certainty, there is no evidence to even suggest, let alone prove, a link between gabapentin and increased risk of suicide or suicide attempt.

DATE: December 20, 2007



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